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On 13 June 2008

TOWNSEND and TOWNSEND and CREW LLP

By: Malinda Adagit

PATENT
Attorney Docket No.: 02307O-067720US
Client Ref. No.: 96-215-3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5513
LALEH SHAYESTEH et al.	Examiner: Jehanne Souaya Sitton
Application No.: 08/905,508	Technology Center/Art Unit: 1634
Filed: August 4, 1997	DECLARATION UNDER 37 CFR 1.132
For: GENETIC ALTERATIONS ASSOCIATED WITH CANCER	
Customer No.: 20350	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Joe W. Gray, am Director, Division of Life Sciences, Lawrence Berkeley National Laboratory and an Adjunct Professor of Laboratory Medicine at the University of California San Francisco. I am a co-inventor of the subject matter disclosed and claimed in the above-referenced patent application.

2. This declaration follows my declaration filed January 8, 2007 relating to the obviousness rejection over Bonjouklian, *et al.* (U.S. Patent No. 5,378,725) that also cites Arnold, *et al.* (*Genes, Chromosomes, and Cancer* 16:46-54, 1996) and Volinia, *et al.* (*Genomics* 24:472-477, 1994, "Volinia") and is in response to the May 10, 2007 Office Action. My background is described in the previous declaration.

3. I have read and am familiar with the contents of the above-referenced patent application and claimed subject matter. I understand that the Examiner has maintained the

rejection of the claims for obviousness based on the same sets of references. My previous declaration summarizes the references and rejections.

4. It is my understanding that the Examiner has questioned my statement that the presence of a gene in an amplified chromosomal region does not lead one of skill to conclude that the gene is overexpressed and important in the pathophysiology of ovarian cancer.

5. This declaration provides additional evidence that one of skill in the art would not conclude that expression of a particular gene would be increased simply based on the observation that the gene is present in an amplified chromosomal region, as well as evidence that one of skill in the art would not conclude, based on the observation that a particular gene is overexpressed, that it would contribute to the pathophysiology of the disease. In support of this contention, I refer to Chin *et al.* (2006) *Cancer Cell.* 10:529-41. [**Exhibit A**], Cheng *et al.,* (2004) *Nat Med.* 10:1251-6 [**Exhibit B**], Eder *et al* (2005) *Proc Natl Acad Sci U S A.* 102:12519-24 [**Exhibit C**], Nanjundan *et al.,* (2007) *Cancer Res.* 67:3074-84 [**Exhibit D**] and a Table of gene expression values from the regions of amplification at 3q26 in ovarian cancer [**Exhibit E**].

6. Chin addresses the issue of whether amplification of a gene correlates with increased expression. In doing so, the authors carried out comparative genomic hybridization (CGH) and gene expression analysis with breast cancer samples. As stated on the bottom of page 531 *"We tested associations between copy number and expression level for 186 genes in regions of amplification at 8p11-12, 11q13-q14, 17q11-12,and 20q13, and we identified 66 genes in these regions whose expression levels were correlated with copy number (FDR <0.01, Wilcoxon rank-sum test; Table 3). These genes define the transcriptionally important extents of the regions of recurrent amplification."* This reference in a top rank scientific journal demonstrates that, in reality, amplification of a chromosomal region does not lead one of skill in the art to conclude that a gene present in the amplified region is over expressed.

7. The Examiner cites Arnold *et al.*, which describes amplification of chromosome 3q26- 3qter in ovarian cancers. It is my understanding that the Examiner believes that there only 30- 50 genes in the region identified by Arnold *et al.* The Examiner contends that, given a finite number of identified, predictable solutions, a person of ordinary skill would

have good reason to pursue known options, and that this would represent nothing more than ordinary skill and common sense.

8. In my last declaration, I referred to the region of 3q26- 3qter as containing many genes. Provided herewith is a printout of information from the Ensembl genome browser that provides more detailed information as to the number of genes that have been identified in this chromosomal region. **Exhibit F** provides a graphic of the region of chromosome 3 from q26.1 through q29. **Exhibit F** also shows the gene contained within this region (Chromosome 3 162152104-199501827), of which there are hundreds. **Exhibit G** focuses on the 3q26 region, 3q26.1 through 3q26.33. A listing of the genes identified in that region (Chromosome 3 162152104-184145606) shows that there are over 80 genes in this region alone. Accordingly, the region identified by Arnold *et al.* as amplified in ovarian cancer, 3q26-3qter, in fact does contain a multitude of genes. This is further supported by **Exhibit E** which describes unpublished work from my laboratory in which demonstrates that the region of amplification at 3q26 that we identified as amplified in ovarian cancer encodes at least 68 genes. Of these, only 30 have expression levels that are associated with copy number ($p<0.05$, univariate t test).

9. The genes in this amplified region could not be characterized as "predictable solutions" to the problem of identifying and treating ovarian cancer. The functions of most of these genes in ovarian cells, and their roles in abnormal ovarian cancer cells, is not known. One of skill would not have a reasonable expectation that any of the genes in this region would necessarily be involved in ovarian cancer.

10. Regardless of how many genes are present in this region, one of skill could not conclude that amplification of *PIK3CA* in this region would lead to overexpression of *PIK3CA* and activation of phosphoinositide-3 kinase signaling. This stems from two facts:

(a) Transcriptional up regulation of a gene frequently does not lead to increased protein expression. We demonstrated that increased transcription of PIK3CA is associated with increased protein levels.

(b) The protein encoded by PIK3CA, the p110alpha catalytic subunit of phosphatidylinositol 3-kinase, must act in concert with the p85 adapter protein encoded by the gene PIK3R1. One skilled in the art would not conclude that expression of one subunit of a

signaling complex would necessarily lead to increased activity of the complex. We demonstrated that amplification and over expression of PIK3CA is associated with increased PI3-kinase activity AND that treatment with the PI3-kinase inhibitor LY294002 decreases proliferation and increases apoptosis. These studies, in combination, demonstrated the importance of *PIK3CA* as an oncogene that is a therapeutic target in ovarian cancer.

11. The publications of Cheng, Eder and Nanjundan indicate that other genes in the 3q26 amplification also play roles in the pathophysiology of ovarian cancer. These studies warranted publication in high rank journals. This again demonstrates the fact that simple presence in a region of amplification is not sufficient to lead one skilled in the art to conclude that the gene contributes to the pathophysiology of the cancer in which it is amplified, and it does not lead one with skill in the art to conclude that it is a useful therapeutic target.

12. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon.

Dated: 6/13/08

Joe Gray, Ph.D.